

## **The Development of Bioenergetics**

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Living systems, being built of matter, and being driven by energy, their analysis can be approached from two sides: that of matter or from the side of energy. This division is analogous to the division into structure and function, or, anatomy and physiology. This division may be very convenient but is artificial, and exists only in our mind, not in nature. Structure and function, essentially, are identical, two sides of the same coin. Structure generates function and function generates structure. A deeper understanding can be achieved only by a fusion of the two.

The basic blueprint of bioenergetics is laid down, and progress can be expected rather in the development in details than in the discovery of new principles. What I would like to see is a more philosophical attitude. "Philosophy" means the search for deeper and wider relations. Needless to say, a philosophical approach presupposes the knowledge of the details, and so it is no wonder that we should have lost ourselves in details. All the same, the loss of a philosophical attitude is regrettable and is characteristic for the contemporary biology. The word "Science", with its present meaning, is of recent origin. In the last century "natural philosophy" was used instead, which indicates a different attitude.

If I were a newcomer in Bioenergetics, I would start my research with trying to clear my mind about the meaning of the word "energy". Living systems consist of atoms, and atoms are, essentially, a cloud of electrons held together by nuclei. So energy can be only electronic energy. Kinetic energy plays no major role in biology except in activation. The source of our energies are the foodstuffs, and their energy can be only electronic. So my first question would be how an electron can release energy? Strictly speaking, electrons have no energy, so how can they release any?

In trying to answer this question I would take my refuge to the table of atoms of Mendeleef. It contains all the atoms out of which

living systems are built. On its left side are the atoms which tend to give off electrons to approach the noble gas structure, while on the right are the atoms which tend to take up electrons. A "trend to give off electrons" involves that the electrons are loosely held, given off easily, that is have a low ionization potential, are on a high energy level. The "trend to take up electrons" means that there are low energy levels capable of accommodating electrons. It follows that energy can be released by electrons of an element of the left side by interacting with an element of the right. In such interaction the electrons of the former could go to a lower energy level of the latter and doing so, would release energy.

What would probably strike me when taking a second look at this table, is the extraordinary nature and position of H. It is a group by itself. This atom is the only one which has the qualities needed to support life. It is small, it parts easily with its electron and the proton, left behind, can merge with the proton pool of the general solvent, water. From this pool an electron can easily pick up a proton and form an H with it. This would lead me to the conclusion that H had to be the fuel of life. Looking over the elements of the right side I would soon come to the conclusion that for many reasons oxygen only is fit to act as general H- or electron-acceptor. However, the acceptor qualities are not as specific as the donor ones, and in absence of O<sub>2</sub> various other elements may also act as acceptors, and, evidently, had to do so before O<sub>2</sub> appeared in the atmosphere. About the possibilities of storage of H, the Mendeleef table would tell me that only C, with its position in the middle, is fit to build up the complex molecules which could hold the H's.

If energy production only demands the interaction of an element from the left of Mendeleef table with an element of the right, then why do not all atoms of the left side simply unite with the atoms on the right side? Why do not all thermodynamically possible reactions take place spontaneously? Should this happen then the whole biosphere would burn up and there would be no place left for life, since no life can exist without energy. Whatever the living machinery does, it has to pay for it in terms of energy. Thus why do all thermodynamically possible reactions not take place? Where is the "hang-up" which makes life possible, and how can life make the reactions go which do not take place spontaneously?

The hang-up is the activation energy, the fact that most chemical reactions are, in a way, similar to a rock on the mountain side. By rolling down, the rock would liberate great amounts of energy. If it does not do so this is simply because in order to roll down it would have to be loosened up, which demands a relatively small quantity of energy which has to be invested. This small initial investment is

which holds reactions up and makes life possible. What life does is to "loosen up" H atoms, decrease the activation energy to a level at which the energy of heat agitation is sufficient to make the reaction go. This loosening up, this decrease of activation energy, is done by enzymes, dehydrogenases, or "H-activation".

With these factors in mind I would try to follow the road on which life has built its machinery. Life builds gradually and does not reject what it has built but builds on top. Consequently, the present cell is comparable to an archeological excavation site where one can find all successive layers on top of one another, the oldest one the deepest. It is like a pyramid. The oldest ones can be expected to be most widely spread and anchored most firmly. By this I mean that the newer a process, the more fancy its chemical equipment, the easier it will be discarded, while the older and simpler ones will be retained more tenaciously. For example: the most complete and newest energy producing machinery is that of biological oxidation. It demands an involved chemical structure. If the cell divides it has to liquify and has to give up its complex solid structures. So it gives up biological oxidation and reverts for energy production to older and simpler processes.

If we try to go back to the very beginning, the prebiotic period, there we find a "primordial soup" with organic molecules in it. When life appeared it had to organize part of these molecules into living systems, while the others were used as "foodstuffs", a source of energy. If we imagined two molecules, side by side, a "living macromolecule" and a foodstuff molecule, the question would come up how could the former take energy out of the latter?

According to what has been said before I can see one way only: taking H atoms (or electrons) off the foodstuff molecule. In order to do this the binding of these H's would have to be loosened up, their activation energy would have to be decreased. The H transfer involves the "dehydrogenation" of the foodstuff molecule. Dehydrogenation being the oldest process we find dehydrogenases widely spread in present living systems. They are actually the foundation of our metabolism.

This simple scheme had to be complicated by the problem of storage. Life needs energy all the time, but foodstuffs are accessible only occasionally. The H's or electrons taken off the foodstuff had thus to be stored to be used later according to need. There had to be an H-, or electron pool. As I have pointed out in my book on "The Living State" (now in press)\* one of the most important building blocks of the energy household is an H- or electron pool which plays an important role even today and is, probably, the most

\* Academic Press, New York.

important energy source of the cell during division. In the interphase it is replenished by the dehydrogenases.

Structural organization has three grades. The basic level is that of "constitution", by which we mean how the atoms are put together to a molecule, and how simple molecules are put together to make more complex ones. This putting together results in fibrous protein molecules. On the second level of organization this fiber is folded up in a meaningful way and a globule is formed. This second step of organization can be destroyed by heating. For complete destruction mostly heating to 100°C at pH 4 is needed. The third level of organization, which I call "coordination", consists of putting together the single globules in a meaningful way so that chain reactions can smoothly take place. This subtlest and highest level of organization can be disturbed most easily, even by moderate heating. It is remarkable that at this highest level of molecular organization the units are put together two-dimensionally, into membranes. It seems likely that only in a two-dimensional structure can the sequence of chemical reactions be controlled and determined by structure.

The history of bioenergetics probably consists of three periods, based on three discoveries of Nature. In the first of them H's were taken off from the foodstuff molecules, to be coupled subsequently to elements, or atomic groups, of the right side of the Mendeleef table (e.g.  $\text{NO}_3$ ). This archaic method involved, possibly, only conformation. The second period of bioenergetics may have been based on the discovery that energy can be derived from another molecule by reshaping its constitution to a form in which it contained less energy, the energy difference being stabilized and transferred by means of "high-energy-phosphate bonds". This led to fermentation. The third discovery which opened the way to the formation of the more complex forms which demanded more energy was the discovery, made by Nature, that the energy of solar radiation could be used to separate H from O, splitting water, the H being used as energy source, and O being sent back as  $\text{O}_2$  into the atmosphere. The energy of H was released gradually in a complex chain of reaction, being transduced into  $\sim P$ , or being stored in the form of foodstuffs. This method demanded a highest level of organization which I called "coordination". This method of energy release and storage became possible only after  $\text{O}_2$  appeared in the atmosphere and could be used as final H- or electron acceptor.

Anaerobic bacteria may be left-overs of the first period.